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WHAT'S KNOWN ON THIS SUBJECT: Approximately 80% of all preterm children are born moderately preterm (32–36 weeks' gestation). Moderately preterm children are at increased risk for developmental delays, but the specific neuropsychological functions that may underlie these delays are unknown.

WHAT THIS STUDY ADDS: Moderately preterm birth is associated with poorer performance in intelligence, attention, visuospatial reasoning, and executive functioning. Using gender-specific norms, our data suggest that preterm boys catch up, whereas preterm girls lag behind their peers at 7 years of age.

abstract

OBJECTIVE: To compare neuropsychological functions in moderately preterm (32–35 weeks' gestation) and full-term children at the age of 7 years and identify gender differences.

METHODS: Community-based prospective cohort study of 248 moderately preterm children (138 boys) and 130 full-term children (58 boys). Neuropsychological tests included IQ, memory, attention, visual perception, motor skills, visuomotor skills, and parental report of executive functioning.

RESULTS: The moderately preterm group performed significantly worse on total and performance IQ, visuospatial reasoning, attention control, inhibition, and executive functioning. No differences were found in verbal IQ, verbal memory, and visuomotor and motor skills. Preterm children were at higher risk for scores <10th percentile on intelligence, visuospatial reasoning (relative risk ratio both: 1.69 [95% confidence interval: 1.29–2.28]), and executive functioning problems (relative risk: 1.94 [95% confidence interval: 1.51–2.57]). Using gender-specific norms, preterm boys performed significantly worse than full-term boys on visuospatial reasoning ($P < .01$); preterm girls performed significantly worse than full-term girls on visuospatial reasoning, intelligence, attention, and executive functioning ($P < .05$).

CONCLUSIONS: Moderately preterm birth is associated with lower intelligence and poorer neuropsychological functioning at early school age. No differences in motor skills and verbal memory were found. Using gender-specific norms, our data suggest that moderately preterm boys catch up, whereas moderately preterm girls lag behind their peers on various neuropsychological functions by the age of 7 years. *Pediatrics* 2012;130:e838–e846

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KEY WORDS

neurodevelopment, cognition, motor skill, moderately preterm, gender, school age

ABBREVIATIONS

ANOVA—analysis of variance
BRIEF—Behavior Rating Inventory of Executive Functions, Dutch version
CI—confidence interval
GA—gestational age
Lollipop—Longitudinal Preterm Outcome Project
PIQ—performance IQ
RR—relative risk
TIQ—total IQ
UMCG—University Medical Center of Groningen
VIQ—verbal IQ

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Moderately preterm infants born at ≥32 weeks' gestational age (GA)[1] currently make up over 80% of all preterm births in developed countries.[2] Approximately 7% of all births in Europe (6.3% in the Dutch population) and 10% in the United States are moderately preterm, and the incidence is rising.[3,4] Although moderately preterm infants seem to be almost fully developed, studies reveal a greater risk for mortality and morbidity than full-terms associated with immaturity-related complications.[5] The increased risk for medical complications has fueled concern about the long-term outcome after moderately preterm birth.[6] In infants born very preterm (GA <32 weeks), neurologic and physiologic immaturity has been associated with clear deficits in a number of key neurodevelopmental areas in childhood.[7,8] These deficits have been associated with poorer school performance.[9] Although more mature than infants born very preterm, moderately preterm-born infants are considerably less mature than infants born at full-term.

The brain almost doubles in size in the 8 weeks before full-term age as differentiation proceeds throughout the cortex and myelination of central brain regions continues.[10] This may increase the risk for disruptions of brain growth and development in preterm-born infants. Evidence has been accumulating that behavioral problems,[11] neurodevelopmental delays or deficits,[6,12–16] and learning difficulties[17,18] occur more frequently in children born between 32 and 36 weeks' GA. Neuropsychological outcome at preschool age has been investigated in 3 cohorts of moderately preterm-born children born in the last 10 years.[12,13,15] Information on outcome at school age in children born in this period is, however, missing. Furthermore, most previous studies used global measures of cognition or school outcome with the result that little is known about the specific neuropsychological deficits that may underlie the global deficits and school performance that have been identified. Because learning is a school-aged child's primary task, we assessed both global intelligence and a range of specific neuropsychological functions in the domains of memory, attention, executive functioning, visuospatial reasoning, and motor skills, which can be considered to be central to effective learning in class.[19]

Finally, although male gender is considered a risk factor in very preterm children,[20] only Romeo et al[12] have addressed the issue of gender differences in outcomes in children born moderately preterm. They found that girls performed better than boys at 12 to 18 months of age, suggesting that male gender is also a risk factor in moderately preterm-born children.[12]

Our aim was to compare moderately preterm-born children with full-term born peers at early school age on neuropsychological and motor outcomes, with particular attention to gender differences.

METHODS

Subjects, Study Design, Sampling Procedure, and Sampling Criteria

The Longitudinal Preterm Outcome Project (Lollipop) is a large, prospective follow-up study on growth, development, and general health in preterm-born children. From a community-based cohort of 45 446 children born in 2002 and 2003 in the Netherlands, 1843 preterm (<36 weeks) and 674 full-term children ($38–41^{+6}$ weeks) were included. Children were recruited from 1 of 13 Dutch preventive child health care centers. GA was calculated from the date of last menstruation, and confirmed in the majority of cases by early ultrasound measurements. Exclusion criteria were major congenital malformations, congenital infections, or syndromes. After each second preterm child was identified, the next full-term born child who did not meet the exclusion criteria was drawn from the same files as a control. Full-term children were thus from the same preventive child health care centers and in the same age range as the preterm children. Sampling procedures, inclusion and exclusion criteria, study conduct, participants and nonparticipants in the Lollipop study have been described in detail elsewhere.[13,21]

For the current study, we selected all moderately preterm-born children ($32–35^{+6}$ GA) and full-term controls ($38–41^{+6}$ GA) from the Lollipop cohort who were currently living in the 3 northern provinces of the Netherlands. This included 341 children born moderately preterm and 195 full-term, age-matched controls. In total, 248 children born moderately preterm (138 boys; 110 girls; median GA: 34 weeks in both groups) and 130 full-terms (58 boys; 72 girls; median GA: 40 weeks in both groups) agreed to participate in this study, a response rate of 73% for children born moderately preterm and 67% for controls. Mean age was 6.9 years (range, 6.4–7.3).

A power calculation had revealed that we needed 250 moderately preterm children and 125 full-term controls to detect a clinically relevant difference in mean IQ, here set at 5 points or one-third of the SD of the IQ-distribution in the population, at $P = .05$ and 80% power. Regarding the power to detect gender differences, we performed a posthoc power analysis. This revealed that we needed 64 preterm boys and 64 girls to detect 5 IQ points difference, being more than half the SD in our sample, as SD of IQ was 9.7 points in our preterm group. A possible explanation of why SD was lower than the expected 15 IQ points is the limited number of IQ subtests used. Thus, the power calculations confirmed the sample size was appropriate for our goals.

Medical data were extracted from hospital charts. Demographic and perinatal data are presented in Table 1. All children had normal or corrected to normal vision. The study was approved by the Ethical Review Board of the University Medical Center of Groningen (UMCG). Examinations were performed in accordance with the institutional (UMCG) and international (Declaration in Helsinki, 1964, European Union Council Directive 86/609/EEC) ethical standards, including written informed consent.

Measures and Procedure

The children and their parents were invited to visit the UMCG or a well-infant clinic in their neighborhood for a 3-hour assessment comprising a number of standardized neuropsychological tests and questionnaires. Each child was tested individually by a trained psychologist who was blind to group assignment while parents completed the questionnaires in the waiting room.

We used a short version of the Wechsler Intelligence Scale, Third Edition, Dutch Version[22] consisting of 2 verbal subtests and 2 performance subtests to estimate total IQ (TIQ), verbal IQ (VIQ), and performance IQ (PIQ). We assessed verbal memory by using the Dutch version of the Rey Auditory Verbal Learning Test.[23] We used the design copying subtest of the Developmental Neuropsychological Assessment battery[24] to assess visuomotor functioning. We assessed the attentional skills that are required for effective functioning at school, using 3 subtests from the Test of Everyday Attention for Children, Dutch version[25]: Map Mission, Score!, and Same world/Opposite world. To measure motor skills required in everyday life, we used the Dutch version of the Movement Assessment Battery for Children.[26] Behavior regulation and meta-cognitive functioning, key aspects of executive functioning, were assessed by using the parent's form of the Behavior Rating Inventory of Executive Functions, Dutch version (BRIEF).[27] A more detailed description of each component of the assessment is provided in Table 2.

Statistical Analysis

χ^2 tests and t tests were used to assess differences between the groups in demographic characteristics. Because the main outcome measures were normally distributed, we used analysis of variance (ANOVA) on all total scores in a 2 × 2 design (preterm versus term; boy versus girl) to detect differences between the groups in neurodevelopmental outcomes. We repeated the analyses adjusting for parental educational level.

Then, to minimize the impact of the gender differences that are often present in typically developing children, gender-specific z scores were computed for each neuropsychological domain for boys and girls separately. The z scores were based on the data of the full-term control groups. ANOVAs were conducted on the gender-specific z scores to investigate differences between preterm and full-term boys, and preterm and full-term girls.

Finally, the prevalence of clinical scores in the different neurodevelopmental domains in the preterm group was investigated. The 10th percentile, defined as a z score below −1.28, was the cutoff.[28] The relative risk (RR) then is defined as the ratio of the percentages of preterm and of term children with a z score below the 10th percentile.

TABLE 1 Demographic and Perinatal Characteristics of the Moderately Preterm and Full-Term Groups

Characteristic	Preterm Group, N = 248	Full-Term Group, N = 130	P
Age, y	6.9 (0.1)	6.9 (0.1)	—
Boys:Girls	138:110	58:72	<.05
GA, wk	33.9 (1.1)	39.7 (0.9)	—
Birth weight, g	2239 (489)	3577 (516)	—
SGA[a] birth weight < 10th percentile	31 (12.5)	11 (8.5)	.352
NICU admission	40 (16.1%)	1 (0.8%)	<.001
Length of hospital admission[b] (d)	19 (12.6) range 0–116	0.4 (1.1) range 0–6	<.0005
Apgar score at 5′ <6 (n = 330)	7 (2.8%)	0 (0%)	.059
Maternal age, y	31.3 (4.4)	31.4 (3.7)	.762
Maternal education level (n = 359)			.064
Low	66 (28%)	21 (17.1%)	—
Middle	92 (39%)	52 (42.3%)	—
High	78 (33%)	50 (40.6%)	—
Paternal education level (n = 350)			.066
Low	78 (34%)	27 (22.5%)	—
Middle	84 (36.5%)	47 (39.2%)	—
High	68 (29.5%)	46 (38.3%)	—

Data are mean (SD) or number or range or percentages (%). P values of the t test and χ^2 test.
[a] SGA, small for GA frequency.
[b] Mean of total hospital admission time including NICU and neonatal ward.

RESULTS

Cognitive and Motor Outcomes in the Preterm and Control Groups

The mean scores are presented in Table 3. The moderately preterm group performed more poorly than the full-term group on every measure. The differences reached statistical significance for TIQ, PIQ, visuospatial reasoning, attention control, and inhibition. On the BRIEF, preterm children's parents reported significantly more difficulty on global executive functioning and the behavioral regulation index but not on the meta-cognition index.

Repeating the analyses with adjustment for parental education level revealed slight increases in most P values but

TABLE 2 Measurements, Related Cognitive and Motor Functions, and Referring Names in the Text

Test/Scale Names	Functions	Referring Name
WISC-III-NL	Short version of Intelligence test	Intelligence
Verbal IQ	Verbal intelligence	VIQ
Similarities	Abstract reasoning	Abstract reasoning
Vocabulary	Comprehension of words	Comprehension
Performance IQ	Performance intelligence	PIQ
Picture arrangement	Chronological ordering	Ordering
Block design	Visuospatial reasoning	Visuospatial reasoning
Total IQ	Global intellectual level	TIQ
AVLT	Verbal memory	Verbal memory
Immediate recall	Short-term memory and learning	Recall
Delayed recall	Active long-term memory	Delayed recall
Recognition	Passive long-term memory	Recognition
NEPSY-2 design copying	Visuomotor functioning	Visuomotor
TEA-Ch-NL	Everyday attention in children	Attention
Map mission	Selective visual attention	Selective attention
Score!	Sustained auditory attention	Sustained attention
Same world	Attention control	Attention control
Opposite world	Response inhibition	Inhibition
BRIEF	Executive functioning in everyday life	Executive function
Behavior regulation index	Modulate and control: inhibition, shift cognitive set, emotional control	BRI
Meta-cognition index	Problem-solving: initiate, working memory, plan/organize, organization of materials, monitor	MCI
Global executive composition	Total of BRI and MCI subscales	GEC
Movement ABC	Motor skills in everyday situations	Motor skill
Fine motor	Manual dexterity	Manual dexterity
Ball	Object control	Object control
Balance	Postural control	Postural control
Total score	Motor proficiency	Total

AVLT, Rey Auditory Verbal Learning Test; BRI, behavioral regulation index; GEC, global executive functioning; MCI, meta-cognition index; Movement ABC, Movement Assessment Battery for Children; NEPSY-2, Developmental Neuropsychological Assessment; TEA-Ch-NL, Test of Everyday Attention for Children; WISC-III-NL, Wechsler Intelligence Scale, Third Edition, Dutch version.

did not affect the statistical significance ($P < .05$) regarding any outcome (Table 3).

Gender Differences

Regarding demographic and perinatal characteristics, no differences existed between boys and girls. Only the numbers of preterm children born small for GA were higher for boys (n = 21) than for girls (n = 8; P = .047). Girls performed significantly better than boys in the areas of verbal memory, visuomotor skills, sustained attention, attention control, and 2 aspects of motor skill: manual dexterity and posture control (Table 4). They also performed better on executive functioning, but the difference failed to reach statistical significance. Boys performed better than girls on visuospatial reasoning, but this difference also did not reach statistical significance. None of the interactions between gender and group was statistically significant.

Adjustment for parental education level hardly affected the P values of the gender differences and did not affect the statistical significance ($P < .05$) of any gender difference (Table 4).

Gender-Specific *z* Scores

Significant differences between preterm and full-term children were more frequent in girls than boys (Fig 1). Z score profiles of the preterm group revealed that preterm boys performed significantly more poorly than full-term boys on only 1 test, visuospatial reasoning ($F_{1,195}$ = 9.82, P = .002, η^2 = 0.048). Preterm girls performed significantly more poorly than full-term girls on visuospatial reasoning ($F_{1,181}$ = 11.35, P = .001, η^2 = 0.059), intelligence ($F_{1,181}$ = 13.12, $P < .001$, η^2 = 0.068), attention ($F_{1,181}$ = 7.14, P = .008, η^2 = 0.038), and executive functioning ($F_{1,181}$ = 9.82, P = .002, η^2 = 0.052). We found a significant group × gender effect for executive functioning ($F_{1,375}$ = 10.67, P = .001, η^2 = 0.028): preterm girls performed more poorly than full-term girls on executive functioning than preterm boys compared with full-term boys.

Relative Risk

Moderately preterm-born children were at higher risk for clinically significant poor (<10th percentile) scores on measures of intelligence, visuospatial reasoning (both RR ratios: 1.69 [95% confidence interval (CI): 1.29–2.28]) and executive functioning (RR: 1.94 [95% CI: 1.51–2.57]).

DISCUSSION

In a detailed investigation of outcomes in a broad range of neuropsychological domains, we found that a moderately preterm group of 7-year-olds scored worse on tests of TIQ, PIQ, visuospatial reasoning, attention, and executive functioning than full-term controls. After adjustment for parental education level, the differences were largest for visuospatial reasoning and executive functioning, up to one-third SD lower, which might not be clinically significant but could be important if magnified to a whole population. The RR of impairment for the moderately preterm children was 1.69 for intelligence and visuospatial reasoning and 1.94 for executive functioning. On tests of VIQ, verbal memory, and visuomotor and motor skills, no differences were found between the groups.

TABLE 3 Cognitive and Motor Results in the Moderately Preterm and Full-Term Groups, Mean Differences, and Statistical Significances of Group Differences Before and After Adjustment for Parental Education

Measures	Preterm Group, *N* = 248 (SD)	Full-Term Group, *N* = 130 (SD)	Mean Difference (95% CI)	*P*	*P*[a]
Intelligence (TIQ)	101.2 (9.7)	103.9 (10.3)	−2.7 (−4.8 to −0.6)	.011	.033
Abstract reasoning, SS	10.8 (2.7)	11.2 (3.1)	−0.4 (−1.0 to 0.2)	.208	.319
Ordering, SS	9.7 (2.9)	10.0 (2.9)	−0.3 (−0.9 to 0.3)	.318	.457
Visuospatial reasoning, SS	9.7 (2.9)	10.8 (3.2)	−1.1 (−1.7 to −0.5)	.001	.004
Comprehension, SS	10.5 (2.4)	10.9 (2.9)	−0.3 (−0.9 to 0.2)	.232	.377
VIQ	103.6 (10.6)	105.7 (13.2)	−2.0 (−4.5 to 0.4)	.108	.184
PIQ	98.7 (12.3)	102.3 (11.8)	−3.6 (−6.2 to −1.0)	.007	.024
Verbal Memory					
Recall	34.3 (8.6)	35.8 (9.5)	−1.5 (−3.4 to 0.4)	.121	.322
Delayed recall	7.4 (2.5)	7.7 (2.7)	−0.3 (−0.8 to 0.3)	.340	.678
Recognition	27.9 (2.8)	28.1 (2.1)	−0.2 (−0.8 to 0.3)	.432	.410
Visuomotor	8.1 (2.2)	8.4 (2.5)	−0.3 (−0.8 to 0.2)	.188	.389
Attention					
Selective attention	11.9 (4.7)	12.7 (4.6)	−0.8 (−1.8 to 0.2)	.129	.142
Sustained attention	6.4 (2.4)	6.8 (2.1)	−0.3 (−0.8 to 0.2)	.192	.375
Attention control	36.9 (10.7)	34.2 (8.6)	2.7 (0.6 to 4.9)	.013	.048
Inhibition	49.5 (19.5)	44.4 (11.7)	5.1 (1.5 to 8.8)	.006	.021
Executive functions					
GEC	104.1 (22.3)	99.3 (19.7)	4.7 (0.2 to 9.3)	.042	.048
BRI	40.0 (9.8)	37.6 (9.0)	2.4 (0.4 to 4.5)	.020	.020
MCI	64.1 (22.3)	61.8 (12.8)	2.3 (−0.7 to 5.3)	.127	.149
Motor skills					
Total	4.7 (5.0)	4.3 (4.2)	0.3 (−0.7 to 1.4)	.497	.742
Manual dexterity	1.2 (2.0)	1.0 (1.5)	0.2 (−0.2 to 0.6)	.254	.381
Object control	2.0 (1.1)	2.0 (2.1)	0.0 (−0.4 to 0.4)	.962	.817
Posture control	1.5 (2.5)	1.3 (2.1)	0.2 (−0.3 to 0.7)	.502	.569

Data are mean (SD). *P* values of the F tests in ANOVA. Higher scores represent better performance on the subtests, except for Attention control, Inhibition, all Executive functioning and all Motor skills, where higher scores indicate poorer performance. BRI, behavioral regulation index; GEC, global executive functioning; MCI, meta-cognition index; SS, standard score (mean = 10; SD = 3).

[a] *P* values adjusted for parental education in ANOVA.

When using raw scores, there were no gender differences in the differences between moderately preterm and term children (ie, no statistically significant gender × GA interaction). Moderately preterm boys and girls performed equally poorer than their full-term counterparts for all outcomes. This is consistent with previous studies.[12,29] However, when using gender-specific norms, preterm boys performed poorer than full-term boys only on the test of visuospatial reasoning, whereas preterm girls performed significantly worse on tests of visuospatial reasoning, intelligence, aspects of attention, and executive functioning than full-term girls.

We identified differences in both global and specific neuropsychological functions. First, consistent with previous studies,[6,12,15] we found small but significant differences between moderately preterm and full-term children in global intelligence. In very preterm children without serious neurologic complications, the severity of impairments is associated with declining GA.[29] In a study of 7- to 9-year-old moderately preterm children, van Baar et al[6] found scores within the normal range, but on average 3 IQ points lower than full-term controls. In our study, although their scores were in the normal range, the preterm children as a group scored 2.7 IQ points lower than full-term age-mates. Unexpectedly, the difference in TIQ scores between preterm and full-term children was greater for girls than for boys: 4 vs 2 points. Male gender is considered a risk factor in very preterm children.[9,12,20] Romeo et al[12] found that girls performed better than boys on the mental developmental index at 12 to 18 months, suggesting that male gender is also a risk factor in late preterm (between 34 and 36^{+6} GA) preschool children. However, at early school age, we found no difference between girls' and boys' performances in the moderately preterm group for TIQ. Further, intelligence scores were significantly lower in the preterm girls than in the full-term girls, whereas they did not differ between preterm and full-term boys. The absence of the advantage of the preterm girls over preterm boys at school age, and the differences between their performance and that of the full-term girls suggest that the moderately preterm boys catch up and/or the moderately preterm girls lose some of their advantage on measures of global intelligence, falling behind full-term girls by early school age.

Second, we found that the moderately preterm group performed considerably more poorly on PIQ and visuospatial reasoning. The block design subtest assessing visuospatial reasoning is a multidetermined subtest, because its score depends on various functions including visuospatial reasoning and fine motor control. As noted above, motor and visuomotor scores did not differ between the 2 groups, indicating that the basis for the difference was poorer visuospatial reasoning rather than poorer motor skills. Given Baron et al's[15] finding of poorer visuospatial reasoning in a group of preschoolers born between 34 and 36 weeks' GA, and our finding of a similar deficit in 7-year-olds born between 32 and 36 weeks' GA, we suggest that poorer visuospatial reasoning persists at least until early school age. Visuospatial reasoning is an indicator of nonverbal abilities, and many preterm children display nonverbal learning disabilities.[29] The effects of this type of

TABLE 4 Cognitive and Motor Results in the Moderately Preterm and Full-Term Groups by Gender, and Statistical Significance of Gender Difference After Adjustment for Gestational Age Category, and After Adjustment for Gestational Age Category and Parental Education

Measures	Preterm, *N* = 248 (SD)	Full-Term, *N* = 130 (SD)	F	*P*	F[a]	*P*[a]
Intelligence (TIQ)						
Boy	101.9 (10.4)	103.8 (9.8)	.763	.383	1.226	.269
Girl	100.4 (8.7)	104.1 (10.7)	—	—	—	—
Abstract reasoning, SS						
Boy	11.1 (2.7)	11.0 (3.0)	.406	.524	.659	.417
Girl	10.6 (2.6)	11.4 (3.1)	—	—	—	—
Ordering, SS						
Boy	9.7 (3.0)	9.7 (3.2)	.953	.330	.653	.420
Girl	9.8 (2.8)	10.3 (2.5)	—	—	—	—
Visuospatial reasoning, SS						
Boy	9.9 (3.2)	11.2 (3.4)	2.972	.086	3.679	.056
Girl	9.5 (2.5)	10.5 (2.9)	—	—	—	—
Comprehension, SS						
Boy	10.6 (2.3)	10.9 (2.9)	.299	.585	.302	.583
Girl	10.5 (2.4)	10.8 (3.0)	—	—	—	—
VIQ						
Boy	104.4 (10.9)	105.5 (12.7)	.666	.415	.991	.320
Girl	102.7 (10.2)	105.8 (13.7)	—	—	—	—
PIQ						
Boy	99.2 (13.2)	102.3 (12.8)	.447	.504	.727	.394
Girl	98.0 (10.9)	102.2 (11.0)	—	—	—	—
Verbal memory						
Recall						
Boy	33.4 (8.8)	33.0 (8.2)	11.822	.001	12.225	.001
Girl	35.5 (8.1)	38.1 (9.9)	—	—	—	—
Delayed recall						
Boy	7.0 (2.6)	7.0 (2.1)	16.779	<.001	15.411	<.001
Girl	7.9 (2.3)	8.3 (3.0)	—	—	—	—
Recognition						
Boy	27.4 (3.3)	27.7 (2.1)	10.979	.001	11.626	.001
Girl	28.4 (1.9)	28.4 (2.0)	—	—	—	—
Visuomotor						
Boy	7.6 (2.1)	7.8 (2.5)	19.525	<.001	17.532	<.001
Girl	8.7 (2.2)	8.9 (2.3)	—	—	—	—
Attention						
Selective attention						
Boy	11.8 (4.9)	12.0 (4.2)	1.384	.240	1.541	.215
Girl	12.0 (4.3)	13.3 (4.8)	—	—	—	—
Sustained attention						
Boy	6.1 (2.4)	6.5 (2.4)	9.171	.003	8.401	.004
Girl	6.9 (2.3)	7.0 (1.9)	—	—	—	—
Attention control						
Boy	37.9 (11.4)	36.1 (10.4)	5.716	.017	5.222	.023
Girl	35.8 (9.8)	32.8 (6.7)	—	—	—	—
Inhibition						
Boy	49.9 (14.6)	47.0 (14.5)	1.545	.215	1.289	.257
Girl	49.0 (24.4)	42.3 (8.3)	—	—	—	—
Executive functions (GEC)						
Boy	104.7 (23.3)	104.1 (23.9)	3.094	.079	2.425	.120
Girl	103.3 (20.9)	95.5 (14.6)	—	—	—	—
BRI						
Boy	40.1 (10.3)	39.6 (11.3)	1.797	.181	1.660	.198
Girl	39.9 (9.2)	36.0 (6.2)	—	—	—	—
MCI						
Boy	64.6 (15.1)	64.5 (14.6)	3.195	.075	2.292	.131
Girl	63.4 (13.6)	59.5 (10.7)	—	—	—	—
Motor skills (Total)						
Boy	5.4 (5.6)	5.1 (4.2)	10.314	.001	9.058	.003
Girl	3.8 (3.8)	3.7 (4.2)	—	—	—	—

learning disorder, which is considered to be on a continuum with executive functioning and attention disorders, may hamper academic performance as well as social interactions.[30]

Our moderately preterm children also performed more poorly than their full-term peers on measures of attention control, inhibition, and executive functioning. Previous studies have revealed poorer executive functioning in children born moderately preterm at 4 years of age.[15] Visuospatial, attention, and executive functioning problems have consistently been found in children born very preterm[31–34] and have been associated with white and gray matter lesions.[34,35] We speculate that these lesions are also the basis of the deficits that we found in moderately preterm-born children.[36]

In typically developing children, girls tend to have a general developmental advantage over boys of the same age,[37] particularly in the areas of attention and executive functions.[37,38] In our study, this was indeed the case in the control group but not in the preterm group, where differences in specific domains were more pronounced among girls. This suggests that moderately preterm girls have lost their developmental advantage and perform more poorly than full-term girls and at approximately the same level as moderately preterm boys. A first alternative explanation may be selection bias (ie, above average abilities in our full-term girls). However, this is unlikely because the full-term girls' scores, although above the mean for their age, were not significantly higher than the Dutch normative scores. A second alternative explanation may be lower GA in the preterm girls because decreasing GA is associated with neuropsychological deficits.[8] However, this is also unlikely because mean and median GA did not differ significantly between the preterm boys and girls.

TABLE 4 Continued

Measures	Preterm, N = 248 (SD)	Full-Term, N = 130 (SD)	F	P	F[a]	P[a]
Manual dexterity						
Boy	1.7 (2.3)	1.3 (1.6)	20.299	<.001	18.434	<.001
Girl	0.7 (1.5)	0.7 (1.4)	—	—	—	—
Object control						
Boy	2.0 (2.2)	1.9 (2.0)	.069	.793	.00	.983
Girl	1.9 (1.8)	2.0 (2.2)	—	—	—	—
Posture control						
Boy	1.8 (2.7)	1.7 (2.4)	8.064	.005	8.494	.004
Girl	1.1 (2.1)	1.0 (1.8)	—	—	—	—

Data are mean (SD). Higher scores represent better performance on the subtests, except for Attention control, Inhibition, all Executive functioning and all Motor skills, where higher scores indicate poorer performance. F and P values concern gender differences adjusted for (preterm or term) group, derived from F tests in ANOVA. BRI, behavioral regulation index; GEC, global executive functioning; MCI, meta-cognition index; SS, standard score (mean = 10; SD = 3).
[a] F and P values adjusted for parental education.

Adjustment for parental education level hardly affected the size of the differences between the moderately preterm and term group. It also did not alter significance on any outcome regarding gender differences. Previous research has consistently revealed that parental socioeconomic status, in particular parental education level, is positively associated with cognitive development.[13,39,40] This was also the case in our cohort, but parental education level did not confound or mediate any association we found.

An important strength of this study is the direct assessment of a wide range of neuropsychological outcomes, using carefully selected, well-established measures, in a large community-based sample of moderately preterm-born children. A limitation is the use of the BRIEF, a questionnaire measure rather than a direct test of executive functioning. However, we selected the BRIEF because the parents' report covers the child's behavior in daily life evaluated over the previous 6 months. At 7 years of age, this is likely to be a more valid measure than laboratory tasks carried out at a single moment in the child's life.

The neuropsychological domains found to be affected in moderately preterm-born children matched those in very preterm-born children in all areas investigated except visuomotor skills and verbal memory. This suggests that, although less vulnerable than very preterm-born children, moderately preterm-born children are more vulnerable than full-term peers, and that the vulnerability of brain development to the disruptions that may accompany preterm birth persist between 32 and 36 weeks' GA, albeit at a reduced level. Although the differences in performances between moderately preterm born and term-born children were only clinically relevant on measures of visuospatial reasoning and executive functioning, we believe that the consistently poorer performance of the moderately preterm-born group on all measures, which are called on by school learning, may disadvantage them compared with their full-term classmates.

Preterm birth is an increasing public health problem in developed countries.[2,5,6]

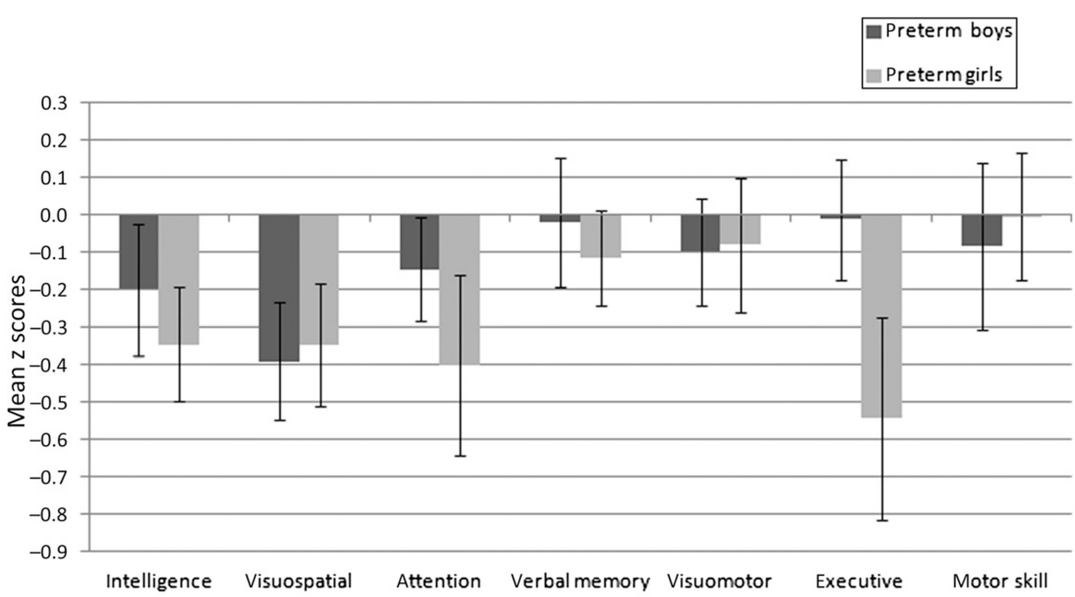

FIGURE 1
The z score profiles with 95% CIs for the preterm boys and preterm girls. Z scores were calculated for the preterm group with reference to the control group data for each gender. The mean z scores for the control group are zero by definition.

Therefore, clinicians and caretakers should be aware that moderately preterm birth significantly affects neuropsychological functioning of at least some of the children involved and may lead to impaired performance at early school age. Moderately preterm girls seem to be more vulnerable at this age. An important question that remains is what explains the gender-differences in the effect of preterm birth on cognitive outcomes and what the underlying mechanisms leading to neurologic impairment may be.

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